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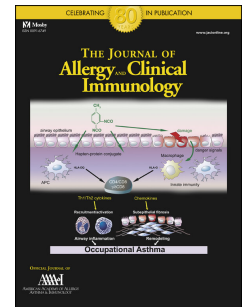
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Understanding the feasibility and implications of implementing early peanut introduction for prevention of peanut allergy

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**Understanding the feasibility and implications of implementing early peanut introduction for
prevention of peanut allergy**

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34 Government's Operational Infrastructure Support Program.

35

36 Abstract

37 Background: A recent randomized trial (the LEAP study) provided evidence that earlier dietary
38 peanut introduction reduces peanut allergy prevalence in high-risk infants. However, questions remain
39 as to how to identify and target the “at risk” population to facilitate timely introduction of peanut

40 Objective: To use population-based infant peanut allergy data to understand feasibility and
41 implications of implementing the LEAP trial intervention

42 Methods: Using the HealthNuts cohort (n=5,300) of 1-year-old infants, we explored the impact of
43 using various criteria to identify infants at high risk of developing peanut allergy, and the implications
44 of skin prick test (SPT) screening prior to peanut introduction

45 Results: Screening all infants with early onset eczema and/or egg allergy could require testing 16% of
46 the population and would still miss 23% of peanut allergy cases. 29% of screened infants would
47 require clinical follow up due to being SPT positive. Around 11% of high-risk infants were excluded
48 from LEAP due to SPT wheal size >4mm to peanut at baseline; data from HealthNuts suggest 80% of
49 these would be peanut allergic on food challenge. There were no life-threatening events among either
50 low- or high-risk infants whose parents chose to introduce peanut at home in the first year of life, or in
51 150 peanut-allergic infants during hospital based challenges.

52 Conclusions: Based on this large epidemiological study, a population program aiming to identify and
53 screen all infants at risk of peanut allergy would pose major cost and logistic challenges that need to
54 be carefully considered. Further research might be required to provide data for low-risk infants.

55 Clinical implications:

56 The LEAP findings are of major significance for the prevention of peanut allergy. The public health
57 and workforce implications of the LEAP study will need to be carefully considered if implemented at
58 the population level.

59 Key words:

60 Peanut allergy; infant feeding; guidelines; skin prick test; specific IgE; prevention

61 Abbreviations:

62 SPT: Skin prick test

63 OFC: Oral food challenge

64 sIgE: Specific IgE

65 LEAP: Learning Early About Peanut Allergy, a randomized trial of peanut consumption compared
66 with peanut avoidance in infants with severe eczema and/or egg allergy for the prevention of peanut
67 allergy

68

69 Capsule summary: Using data from a large epidemiological study, we explore potential criteria for
70 identifying infants at high risk of developing peanut allergy and the implications of skin prick test
71 screening prior to peanut introduction at the population level.

72

73 **Introduction**

74 The recent publication of the LEAP (Learning Early About Peanut Allergy) randomized trial provided
 75 direct evidence in high-risk infants (defined as those with severe eczema and/or egg allergy) that
 76 delayed introduction of dietary peanut increases the risk of peanut allergy.¹ This is the first
 77 randomized trial to describe a prevention strategy for peanut allergy. With reports from the UK, US
 78 and Australia that the prevalence of peanut allergy is around 1-3%,²⁻⁴ and evidence that peanut
 79 introduction is delayed in a high proportion of children in these countries,^{5,6} a shift towards earlier
 80 introduction of peanut in infants is likely to significantly reduce the burden of peanut allergy. How to
 81 achieve this safely and in a cost-effective manner is currently the subject of intense debate.

82 An editorial accompanying publication of the LEAP study suggested “any infant between 4 months
 83 and 8 months of age believed to be at risk for peanut allergy should undergo skin-prick testing (SPT)
 84 for peanut. If the test results are negative, the child should be started on a [peanut containing diet]...
 85 and if the results are positive but show mild sensitivity (i.e., the wheal measures 4 mm or less), the
 86 child should undergo a food challenge” (Gruchalla and Sampson).⁷ However, no published data are
 87 currently available to determine what proportion of the population fall in to the category of “high
 88 risk” (thus how many infants would need SPT), what proportion of the high-risk group will develop
 89 peanut allergy, and what proportion of all peanut allergy cases occur in high-risk compared with low-
 90 risk infants. An additional question that arises from the LEAP study is what proportion of infants with
 91 a greater than 4mm peanut SPT wheal size (the cut-off used in LEAP to define likely peanut allergy)
 92 are truly peanut allergic, and thus whether this group should potentially undergo formal oral food
 93 challenge (OFC) prior to recommending peanut avoidance.

94 Interim guidelines have also been released as a result of the LEAP findings, based on consensus
 95 among multiple allergy organizations worldwide. These recommend introduction of peanut between
 96 4-11 months of age, in infants with severe eczema or egg allergy, in countries where peanut allergy is
 97 prevalent. The guidelines also suggest that infants with severe eczema or egg allergy in the first 4-6
 98 months of life might benefit from evaluation by an allergist or physician trained in management of

allergic disease – including potentially SPT and in-office observed peanut ingestion.⁸ Data characterizing SPT and specific IgE (sIgE) values to peanut in the high-risk population of infants, and their relationship to peanut allergy, may help to define the impact on the allergy workforce if this advice is followed, and inform strategies for determining which infants require supervised peanut challenges. Finally, data on the likelihood of reactions, particularly severe reactions, in young infants exposed to peanut in early life is also likely to be useful in addressing these questions.

In a recent companion study to the LEAP trial, the EAT (Enquiring About Tolerance) randomized trial compared early introduction (from 3 months of age) of allergenic foods including peanut with standard introduction (from 6 months of age) in infants recruited from the general population.⁹ The EAT trial included infants with and without existing allergic disease (eczema) and infants in the control (standard introduction) arm were only required to avoid allergenic foods until 6 months of age. By comparison in the LEAP trial the control arm avoided peanut until age 5 years. Compliance with the intervention in the EAT trial was also lower than in the LEAP trial. There was no evidence of a statistically significant difference in food allergy prevalence at age 1-3 years between the early and standard introduction arms in the primary intention-to-treat analysis. The failure to demonstrate efficacy of early introduction of allergenic foods in EAT could potentially be due to low compliance with the early introduction intervention (consumption of sufficient doses of the allergenic foods), or because the age at allergen introduction in the intervention (median reported age approximately 5 months) and control arms (introduced from 6 months, actual age not reported) might not have been different enough to have a biological impact.

We aimed to use data from the HealthNuts study, a population-based cohort of 5,300 infants in Australia, to understand the implications and generalisability of the LEAP findings regarding introduction of peanut at the population level. The HealthNuts population provides an ideal opportunity to examine these issues, since all infants underwent SPT screening to peanut using the same technique, device and extract used in the LEAP study, and infants with any detectable wheal underwent an OFC to peanut, irrespective of SPT wheal size or history of previous ingestion or reaction, unless a clear reaction had occurred in the past month.

Methods

HealthNuts study population

HealthNuts is a large-scale, population-based cohort study undertaken to assess the prevalence and risk factors for allergic disease in early childhood.^{10,11} Briefly, by using a predetermined population-based sampling frame drawn from local government-led immunization clinics in Melbourne, Australia (population four million), infants were recruited while attending one-year-old immunization. All infants aged between 11 and 15 months (inclusive) were eligible for recruitment (74% response rate). Parents completed a questionnaire prior to SPT that included questions about the child's history of peanut consumption and food reactions, and history of eczema (including whether diagnosed, age at diagnosis and history of medication use).

Infants were skin prick tested to four foods including peanut and hen's egg (ALK-Abelló, Madrid, Spain), with a positive control (histamine 10 mg/mL), and a negative control (saline) using single-tine lancets on the infant's back. All participants with a detectable wheal to one or more foods were invited to a hospital-based clinic where staff administered repeat SPT and diagnostic OFCs, blinded to the infant's SPT wheal size and history of ingestion. A positive challenge was defined based on pre-specified objective criteria¹²: hives (3 or more hives lasting at least 5 minutes); vomiting; angioedema or anaphylaxis (evidence of circulatory or respiratory involvement), occurring within 2 hours of ingestion of the food. We chose any detectable wheal size as our entry criterion to assess the food allergy status of participants to minimize the chances of missing cases of food allergy. A random sample of infants with negative SPT results was also invited to undergo a food challenge (negative controls for the clinic study). SPT was performed with peanut extracts purchased from the same company employed in the LEAP study (ALK-Abelló) and the same lancet device. Blood samples were obtained at clinic attendance and total and sIgE levels to peanut, egg, and other relevant foods based on clinical history, were measured using ImmunoCAP System FEIA (Phadia AB, Uppsala, Sweden).

Ethics

Ethical approval was obtained from the Office for Children Human Research Ethics Committee (HREC; ref no CDF/07/492), Department of Human Services HREC (ref no 10/07), and Royal Children's Hospital HREC (ref no 27047). Parents/guardians of all participants provided written informed consent.

Definitions

Eczema in the first year of life was defined as a diagnosis of eczema, to identify those infants who would already be identified through the medical system.

Early moderate/severe eczema was defined as diagnosed eczema starting in the first 6 months of life and treated with topical steroids (either over-the-counter or prescribed). Severity of eczema is defined variably with SCORAD or by ill-defined doctor specific grading so for the purposes of this analysis, we used early onset eczema (before 6 months) and requirement for topical steroid therapy to identify more severe eczema. This would also offer a consistent approach to identifying these infants in practice if the international consensus recommendations are to be adopted.

Egg allergy was defined as challenge-proven egg allergy at 1 year of age, in the presence of sIgE to egg detected either by SPT (wheal size \geq 2mm above saline control) or serum sIgE levels (\geq 0.35kUA/L).

Peanut allergy was defined as challenge proven peanut allergy at 1 year of age. All infants with a positive peanut challenge had peanut sIgE detected by either SPT or serum sIgE.

The following definitions were used for risk stratification:

High-risk infants were defined as those with either egg allergy or early onset (\leq 6 months) moderate/severe eczema – these infants would potentially have been eligible for inclusion in the LEAP study,¹ depending on the age of manifestation of egg allergy and the severity of eczema. A comparison of definitions of high risk used in LEAP and accompanying editorial and consensus guidelines is presented in Supplementary Table S1.

Low-risk infants were defined as those with no egg allergy and no early onset (≤ 6 months) moderate/severe eczema. It should be noted that this category of infants includes those with late onset or mild forms of eczema.

Statistical methods

We calculated the proportion of participants in the HealthNuts cohort who: (1) were classified as “high risk” and “low risk”; (2) had challenge-proven peanut allergy in each of the high-risk and low-risk groups; and (3) calculated the proportion of all peanut allergy cases that occurred in high-risk and low-risk infants. Proportions were calculated as percentages with 95% confidence intervals calculated assuming a binomial sampling distribution.

SPT wheal sizes and peanut sIgE levels were classified for analysis into groups according to a combination of clinical cut-offs and those used in the LEAP study¹ to define the SPT-Positive group (SPT 1-4mm) and the likely peanut allergy group (SPT >4 mm). Thus SPT results were grouped into 0mm (not sensitized); 1-2mm (SPT-positive according to LEAP but not generally considered sensitized by clinical criteria); 3-4mm (sensitized according to both LEAP and standard clinical cut-offs) and >4 mm (likely peanut allergic according to LEAP). sIgE to peanut was grouped into <0.1 kUA/L (below the limit of detection); 0.1-0.34 (detectable but below usual clinical cut-offs for sensitization); 0.35-17.4 (sensitized) and ≥ 17.5 (high positive). The proportion of positive challenges in each SPT or sIgE category was calculated with 95% confidence intervals as above.

To investigate factors associated with age at introduction of peanut into the infant diet, the cohort was divided into groups according to the risk factors: family history of eczema or food allergy, infant eczema, and infant history of reaction to egg or milk. Challenge-confirmed egg allergy was not used in this analysis because SPT and challenges to egg occurred after parents had already made the decision on when to introduce peanut to their child. Chi-squared p-values were calculated comparing the distribution of age at peanut introduction in each risk group to the baseline group of “no risk factors”.

We modelled the potential proportion of peanut allergy cases in the community that might be prevented by applying the LEAP intervention findings to the general population using the following steps:

1. We used a hypothetical population of 1,000 infants to represent the general population
2. We used the actual prevalence of early onset eczema and/or egg allergy in HealthNuts to split the population into “low-risk” and “high-risk” groups
3. We assumed that the LEAP intervention would only be applied to the high-risk group (as per the current consensus guidelines⁸). We used HealthNuts data to estimate the prevalence of peanut allergy in the low-risk group without intervention (i.e. the HealthNuts observed prevalence of peanut allergy among low-risk infants).
4. We used direct percentages from the LEAP study¹ to estimate the proportion of high-risk infants who would have a SPT>4mm to peanut at 4-11 months of age.
5. We used HealthNuts data to estimate the proportion of infants with a SPT >4mm who would be peanut allergic (80%) as this data was not available from the LEAP study.
6. We used direct percentages from the LEAP control arm to estimate the prevalence of peanut allergy without intervention (17%) and direct percentages from the LEAP intervention arm to estimate the prevalence of peanut allergy with timely peanut introduction between 4-11 months (3%), and thus calculated the proportion of cases that could be prevented.

220 Results

221 *Characteristics of the HealthNuts study cohort*

222 Study participation is shown in Supplementary Figure 1. Relevant characteristics of the HealthNuts
223 study cohort are described in Table 1. Our previous work has shown that the HealthNuts participants
224 are generally representative of the infant population of metropolitan Melbourne as compared to the
225 state-mandated Victorian perinatal database.¹⁰

226 *Proportion of peanut allergy cases in the general population occurring in high- and low-risk infants*

227 Table 2 shows peanut allergy prevalence by eczema and egg allergy status. Overall 84% of the
228 population were classified as “low risk” (no early moderate/severe eczema or egg allergy), with 0.8%
229 of these infants having challenge-confirmed peanut allergy (Table 2). This represents 23% of all
230 peanut allergy cases in the population, who would be missed by targeting only high-risk infants. The
231 remaining 16% of the population were classified as “high risk” by this definition, and 14% of these
232 infants were peanut allergic. This represents 77% of all peanut allergy cases in the population. The
233 highest risk of peanut allergy was in infants with both early moderate/severe eczema and egg allergy
234 (who represented 3.5% of the general population), with 35% of these infants having peanut allergy.
235 Peanut allergy was more common in infants with egg allergy than those without egg allergy,
236 irrespective of their eczema status.

237 *Characterizing SPT and sIgE levels to peanut at the population level*

238 The distribution of SPT wheal sizes and sIgE levels in the cohort are shown in Figure 1. Compared to
239 low-risk infants, high-risk infants were more likely to have a detectable wheal on peanut SPT: 29%
240 (95%CI 25.8, 32.4) vs 4% (95%CI 3.4, 4.7), $p<0.001$. Among high-risk infants with a 0mm SPT to
241 peanut, 34% had detectable levels of sIgE to peanut. No infants with a negative (0mm) SPT or peanut
242 sIgE below the limits of detection had a positive peanut OFC in either the high or low-risk groups;
243 however some positive peanut challenges occurred in infants with a SPT wheal size or sIgE level

below the traditional cut-offs for sensitization (3mm for SPT and 0.35kUA/L for sIgE) (Figure 1c and Figure 1d).

Using the SPT cut-off values defined in the LEAP study as “likely peanut allergy” (SPT wheal size >4mm), 70.3% (95% CI 54.8, 85.7) of low-risk infants and 80.2% (95% CI 73.0, 87.4) of high-risk infants were allergic on OFC (Table 3).

Prevalence and types of adverse reactions to peanut in the first year of life among infants who introduced peanut at home prior to study participation

Overall 30% of infants were introduced to peanut by their parents before 12 months of age (predominantly in the form of peanut butter, data not shown). Infants with eczema or a personal history of reactions to other foods (egg or milk) were less likely to be given peanut before 12 months of age, while a family history of food allergy or eczema had little impact on the age of peanut introduction in the absence of any clinical signs of allergy in the infant (Table 4). Only 13% of infants with both early eczema and a history of reaction to milk or egg were introduced to peanut by 12 months of age.

Of those infants introduced to peanut by their parents by age 12 months, 3% reported a possible reaction, with the majority of these (82%) occurring within 1 hour of ingestion, consistent with IgE-mediated reactions. Reactions occurred more commonly in high-risk infants (10.6% vs 1.4%, $p<0.001$). Table 5 shows the types of reactions. Only one infant had a history consistent with possible anaphylaxis (wheeze/difficulty breathing) with peanut being the reported food causing this reaction (when given at age 12 months), however this child was later shown to tolerate peanut on OFC at age 14 months.

Prevalence and types of adverse reactions to peanut during hospital-based oral food challenge

The most common reaction to peanut OFC, irrespective of SPT wheal size or risk profile, was urticaria (Table 6). Anaphylaxis occurred in 6 challenges (4% of positive challenges), with cases of anaphylaxis seen in both high and low-risk groups.

Applying the proportion of peanut allergy cases that may be preventable by applying LEAP intervention to the general population

We used the best available data from either HealthNuts or LEAP to model the proportion of peanut allergy cases that might be preventable if the LEAP intervention findings were applied to a hypothetical population of 1,000 infants (Figure 2), with the following assumptions:

1. 84% of the population are low-risk and 16% high-risk (HealthNuts data)
 - Of the low-risk infants, 0.8% are peanut allergic without intervention (HealthNuts data)
 - Of the high-risk infants, 89% would have a $SPT \leq 4mm$ and 11% would have a $SPT > 4mm$ if screened at 4-11 months of age (LEAP data). *Note that this is lower than the observed proportion of high-risk infants with a $SPT > 4mm$ in HealthNuts (14.6%), probably because infants in HealthNuts were older (12 months) at time of skin prick test.*
2. 17% of high-risk infants with a 0-4mm wheal would be allergic without intervention (LEAP data – peanut avoidance arm). *Note that this is higher than the observed proportion of high-risk infants with a 0-4mm wheal who are peanut allergic in HealthNuts, possibly because of (1) older age in HealthNuts, and/or (2) earlier introduction of peanut in the HealthNuts cohort compared with the LEAP control arm.*
3. 3% of high-risk infants with a 0-4mm wheal would be allergic with intervention (LEAP data – early peanut introduction arm).

These assumptions were used to calculate the number of cases of peanut allergy in this constructed population that would be expected with and without intervention, and therefore the proportion of peanut allergy cases that could be prevented through the early introduction of peanut. Note that the proportion of cases that would be expected in low- and high-risk infants in this hypothetical population does not match that observed in HealthNuts, because of the differences between LEAP and HealthNuts described in assumptions 1-3 above.

If the LEAP intervention findings were applied to all infants with early onset eczema and/or egg allergy, 44% of all peanut allergy cases in the community might be prevented (Figure 2; $20/45 =$

44%). If the same magnitude of risk reduction (80%; 6 of 7 cases prevented) could be achieved in low-risk infants, a total of 58% of peanut allergy cases in the community might be prevented (26/45 = 58%). This would increase to 64% of cases if timely peanut introduction could also be implemented and was protective in the 20% of infants with a SPT wheal >4mm who are negative on baseline challenge (29/45=64%). If timely peanut introduction was half as successful at preventing peanut allergy in low-risk infants compared to high-risk infants (e.g. 40% of cases prevented instead of 80%), and not implemented in the SPT>4mm group, a total of 51% of peanut allergy cases might be prevented (23/45 = 51%).

304 Discussion

305 Our study extends the findings of the LEAP trial¹ to a population-based cohort. We show that using
 306 the strict criteria applied in LEAP to select high-risk infants to target early introduction of peanut
 307 would miss a sizeable number of peanut allergy cases in the general community. Even using very
 308 inclusive criteria to define “high risk” (all infants with early onset eczema and/or egg allergy) to target
 309 screening, 23% (95% CI 16.6, 31.3) of peanut allergy cases in the population would still be missed.
 310 Furthermore, 29% (95% CI 25.8, 32.4) of these high-risk infants could have a positive SPT. If the
 311 current international consensus guidelines were followed, these infants would require clinical follow
 312 up to assist with assessment for timely introduction of dietary peanut, which is a large proportion of
 313 the general infant population.

314 Using a combination of data from LEAP and HealthNuts to model the potential impact of
 315 implementing the LEAP intervention in the wider population, we show that this might only prevent up
 316 to 44% of peanut allergy cases if the intervention is restricted to high-risk infants. New strategies in
 317 addition to earlier introduction of peanut need to be investigated in future studies to prevent peanut
 318 allergy in those infants whose peanut allergy develops too early to benefit from the early introduction
 319 intervention. Further research to determine whether earlier introduction of peanut is also beneficial in
 320 low-risk infants may also be warranted. The recently published EAT trial compared peanut
 321 introduction (along with other allergenic foods) from 3 months (although actual reported median age
 322 at introduction was around 5 months) with introduction after 6 months of age in population-recruited
 323 infants (with and without eczema). The primary analysis (intention to treat) showed no significant
 324 difference in peanut allergy in the two groups, although there was a lower prevalence of peanut
 325 allergy in the early introduction group in a secondary per protocol analysis. High- and low-risk infants
 326 were not analysed separately.⁹

327 We add to the findings of the LEAP trial by showing that around 80% (95% CI 73.0, 87.4) of high-
 328 risk infants with a SPT wheal size >4mm, excluded from participation in LEAP, had challenge
 329 confirmed peanut allergy. Conversely, 20% of infants with a SPT wheal size >4mm could tolerate

peanut. Thus if screening were implemented and this cut off used, an inappropriate recommendation to avoid peanut might be made for these high-risk infants. Identifying peanut tolerant infants through peanut OFC so that they can be included in the earlier introduction of peanut group could improve the proportion of peanut allergy cases prevented, although no data are currently available on the potential beneficial effect of early peanut introduction in preventing peanut allergy later in life in infants with such size SPT. If a cut off is to be used to identify infants who are highly likely to be peanut allergic, and thus reduce the need for food challenges, a more appropriate level might be wheal sizes of 8mm or greater, which has previously been shown to have a 95% positive predictive value for peanut allergy in infants.¹³

Our results obtained from a general population cohort also confirm other findings from the high-risk LEAP cohort. We showed that even high-risk infants with SPT wheal sizes of 1-4mm are likely to tolerate peanut if introduced early in life. We also found that positive challenges occurred in some infants with a peanut SPT wheal size of 1-2mm, below the traditional cut-off of 3mm, and in infants with a peanut sIgE level between 0.1-0.34. A further interesting confirmation of the LEAP study was the finding that 34% of high-risk infants with a 0mm SPT to peanut had detectable levels of peanut sIgE – in the LEAP cohort 28% of SPT negative infants had detectable peanut sIgE.¹

The strengths of this study include the careful peanut allergy phenotyping of a large cohort of infants through hospital supervised OFCs, and the fact that the same SPT device, commercially available allergen extract and OFC methodology as LEAP were used. In this context it is striking that predictive values for peanut allergy in the <4mm SPT group were consistent across both studies, despite one study being only high-risk infants and the other population based, with two independent study teams performing the testing. If SPT is to be considered for screening it is therefore likely to be a robust methodology.

The findings of this study are likely to be generalizable to the wider Victorian population due to the population-based sampling frame and high participation rate. We have evidence that study participants are generally representative of all births in Victoria from data collected routinely in the

perinatal database.¹⁰ In addition, we have previously shown that weighting prevalence estimates, using data on the prevalence of risk factors for peanut allergy in all eligible infants whose parents declined study participation, only marginally altered the prevalence estimate for peanut allergy from 3.0% to 2.9%.²

Despite the large sample size of this study, peanut allergy is a relatively uncommon outcome in the general population. As a result, some SPT and sIgE groups only include a small number of infants, resulting in wide confidence intervals. Our findings need to be interpreted in conjunction with the magnitude of uncertainty around each of the reported estimates.

Limitations include that although study participants were peanut challenged within 4-8 weeks of their screening SPT at their 12 month immunization visit, our results pertain to children 12-18 months which is an older age group than that recruited into LEAP. However, despite the difference in age range, key results are remarkably similar across the two cohorts. Additionally different definitions of eczema were used across the cohorts, with infants included in LEAP likely representing more severe eczema cases. Both definitions have limitations since both incorporated the somewhat subjective criteria of parental report of eczema severity and topical steroid use. Defining eczema severity remains problematic so we chose a definition that would identify infants who would be seen through the medical system, with early onset and requirement for topical steroid therapy used to identify more severe eczema. This would also offer a consistent approach to identifying these infants in practice if the international consensus recommendations are to be adopted. Restricting the definition to capture only more severe cases of eczema would increase the number of peanut allergy cases missed.

What are the implications of our findings for clinical practice and the potential to implement screening guidelines? As reported in other population-based studies of infants, eczema and egg allergy are common in infancy,^{2,14,15} although egg allergy appears somewhat more common in Australia than in Europe¹⁶; thus even if only high-risk infants were targeted a relatively large proportion of the population would require screening at least in some countries. Consistent with previous studies,¹⁷ we show that both SPT and sIgE to peanut have a strong negative predictive value.

Screening could therefore potentially include some testing in the community setting using peanut sIgE blood tests, perhaps in combination with Ara h2 as a second step,¹⁸ making screening more feasible and reducing the number needing SPT and/or OFC. Furthermore egg allergy was a stronger predictor of peanut allergy than eczema alone; however since less than 25% of infants had introduced egg by 6 months of age, this is unlikely to be a helpful early marker for targeting early onset allergic disease for screening as recommended by consensus guidelines.⁸ Further studies will need to be done to investigate the potential implications of implementing screening in other countries including the US, which may have different rates of eczema and peanut allergy.

An alternative paradigm to screening high-risk infants would be to recommend timely introduction of peanut for all infants irrespective of allergy risk, as per the current Australian guidelines.¹⁹ Our findings provide some reassurance that reactions at home when peanut was introduced as part of a weaning diet before 12 months were uncommon overall, with no (clear) cases of anaphylaxis reported. However, there was evidence of self-selection based on risk, whereby infants with eczema or egg allergy were less likely to introduce peanut before 1 year of age – and this group were more likely to react on introduction – thus it is difficult to predict whether severe reactions would have occurred in peanut was introduced to all high-risk infants at home in an uncontrolled manner. The fact that peanut-allergic infants usually had mild reactions during supervised challenges provides some reassurance. While LEAP did not look at whether early introduction of peanut in low-risk group might lead to reduced risk of peanut allergy, this may be a reasonable recommendation for the population, since data from HealthNuts suggest likelihood of reaction is low and reactions were mild-moderate. The publication of the LEAP trial, resulting media coverage, and release of international consensus guidelines stating that delay in peanut introduction might be harmful, is likely to encourage more parents to introduce peanut earlier in infancy, and the HealthNuts study provides baseline data against which to measure changes in timing of peanut introduction and the resulting impact on peanut allergy prevalence.

We provide data that the majority of reactions on peanut introduction in young infants are mild, irrespective of whether peanut it is introduced at home or in the hospital, and irrespective of SPT

wheal size or clinical risk factors. Caution is needed in interpretation of these results since despite the large population recruited the number of peanut-allergic infants was only 150 cases – more severe reactions might still be observed in rare cases. However, in conjunction with findings from the LEAP study, our findings provide reassurance that introducing peanut in infancy is unlikely to lead to severe reactions. In fact, since infants in HealthNuts were already 1 year of age and had predominantly avoided peanut in infancy, thus increasing their likelihood of being peanut allergic, we would expect to see even fewer reactions if peanut was introduction earlier in the first year of life as in LEAP.

In conclusion, our results show that large numbers of infants would be affected if screening prior to introduction of peanut was implemented; thus careful consideration of whether and how to target and/or screen infants is required before public health recommendations can be made. Despite the potential to substantially reduce the population prevalence of peanut allergy through timely introduction of peanut high-risk infants, around 20% of peanut allergy cases in the population occur in low-risk infants and an additional 20% of cases occur in infants ineligible for participation due to a SPT wheal size $>4\text{mm}$ at recruitment. Additional prevention strategies will be required for these infants. Further population-based intervention trials are required to determine whether timely introduction of peanut is also protective for low-risk infants, and to inform cost-effective analysis of the intervention at the population level as well as cost-effectiveness of various screening strategies.

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Tables and Figure Legends

Table 1: Characteristics of the HealthNuts cohort

| Characteristic | Negative (0mm) SPT to peanut at 12 months | | | |
|-----------------------------------------------------------|--------------------------------------------------|--------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------------------------|
| | Attended HealthNuts clinic as controls* N=197 | Did not attend HealthNuts clinic N=3857 | Attended HealthNuts clinic due to sensitization to other food/s N=428 | Detectable wheal on peanut SPT (≥ 1 mm) and attended clinic N=417 |
| Age (months, SD) at recruitment | 12.6 (0.7) | 12.7 (0.7) | 12.6 (0.7) | 12.7 (0.7) |
| Age (months, SD) at clinic attendance | 14.6 (1.2) | - | 14.4 (1.3) | 14.3 (1.2) |
| Male sex | 48% | 50% | 50% | 60% |
| Eczema [†] | | | | |
| None | 68% | 77% | 55% | 36% |
| Eczema starting ≤ 6 mo treated with topical steroids | 11% | 6% | 20% | 35% |
| Eczema starting ≤ 6 mo no topical steroids | 10% | 6% | 9% | 12% |
| Eczema starting >6 mo of age | 7% | 4% | 7% | 7% |
| Age at egg introduction [†] | | | | |
| ≤ 6 months | 22% | 25% | 18% | 23% |
| 7-12 months | 70% | 68% | 71% | 62% |
| Not yet given | 5% | 3% | 5% | 10% |
| Egg allergic [‡] | - | - | 51% | 47% |
| Peanut sIgE measured | 77% | - | 83% | 86% |
| Peanut OFC completed | 68% | - | - | 90% |

*Negative SPT to all tested foods at recruitment

[†] Percentages may not add up to 100% due to missing data

[‡] Defined as challenge-proven egg allergy at 1 year of age, in the presence of sIgE to egg detected either by skin prick test (wheal size ≥ 2 mm above saline control) or serum sIgE levels (≥ 0.35 kUA/L).

Table 2: Proportion of peanut allergy cases in the HealthNuts population-based sample occurring in high- and low-risk infants

| Clinical profile | Eczema status | Egg allergy | N | Proportion of the population with this risk profile % (95% CI) | Proportion with peanut allergy at age 1 year % (95% CI) | Proportion of peanut allergy cases captured (total n=137 [‡]) % (95% CI) |
|--------------------------------------|-----------------------------------------|-------------|------|-------------------------------------------------------------------|------------------------------------------------------------|---------------------------------------------------------------------------------------|
| Low risk | None | No | 3338 | 72.2 (70.9, 73.5) | 0.6 (0.3, 0.8) | 13.9 (8.6, 20.8) |
| | Later onset or mild eczema [†] | No | 535 | 11.6 (10.7, 12.5) | 2.4 (1.1, 3.7) | 9.5 (5.1, 15.7) |
| | <i><u>Low-risk group: total</u></i> | | 3873 | 83.8 (82.7, 84.8) | 0.8 (0.5, 1.1) | 23.4 (16.6, 31.3) |
| High risk | None | Yes | 167 | 3.6 (3.1, 4.2) | 10.8 (6.0, 15.5) | 13.1 (8.0, 20.0) |
| | Later onset or mild eczema [†] | Yes | 82 | 1.8 (1.4, 2.2) | 20.7 (11.8, 29.7) | 12.4 (7.4, 19.1) |
| | Early moderate/severe eczema* | No | 338 | 7.3 (6.6, 8.1) | 3.8 (1.7, 5.9) | 9.5 (5.1, 15.7) |
| | Early moderate/severe eczema* | Yes | 164 | 3.5 (3.0, 4.1) | 34.8 (27.4, 42.1) | 41.6 (33.3, 50.3) |
| <i><u>High-risk group: total</u></i> | | | 751 | 16.2 (15.2, 17.3) | 13.9 (11.5, 16.5) | 76.7 (68.7, 83.4) |

* Diagnosed eczema starting \leq 6 mths of age & treated with topical steroids

[†] Diagnosed eczema starting > 6 mths of age & treated with topical steroids or eczema (at any age) without topical steroid treatment

[‡] Of the cases that could be classified into high- or low-risk groups (complete data on eczema and egg allergy status)

Table 3: Proportion of positive peanut challenges by skin prick test wheal and specific IgE cut-offs in high- and low-risk populations

| Risk group | SPT wheal size/ sIgE level (kuA/L) | Number of peanut OFC performed | % of peanut OFC that were positive (95% CI) |
|------------------------------------------------------------------------------------------|------------------------------------------|--------------------------------------|---------------------------------------------------|
| Low risk (No early eczema and/or egg allergy) | SPT: 0mm* | 154 | 0% (0, 2.4) [†] |
| | SPT: 1-2mm | 23 | 0% (0, 14.8) [†] |
| | SPT: 3-4mm | 16 | 12.5% (0, 30.7) |
| | SPT: >4mm | 37 | 70.3% (54.8, 85.7) |
| High risk (early eczema [≤ 6 mths, requiring topical steroids] and/or egg allergy) | SPT: 0mm* | 72 | 0% (0, 5.0) [†] |
| | SPT: 1-2mm | 44 | 11.4% (3.8, 24.6) |
| | SPT: 3-4mm | 51 | 5.9% (0, 12.6) |
| | SPT: >4mm | 121 | 80.2% (73.0, 87.4) |
| Low risk (No early eczema and/or egg allergy) | sIgE: <0.1 ** | 131 | 0% (0, 2.8) [†] |
| | sIgE: 0.1-0.34 | 24 | 20.8% (3.3, 38.4) |
| | sIgE: 0.35-17.4 | 51 | 43.1% (29.1, 57.2) |
| | sIgE: ≥ 17.5 | 4 | 75.0% (19.4, 99.4) |
| High risk (early eczema [≤ 6 mths, requiring topical steroids] and/or egg allergy) | sIgE: <0.1** | 31 | 0% (0, 11.2) [†] |
| | sIgE: 0.1-0.34 | 28 | 21.4% (5.2, 37.6) |
| | sIgE: 0.35-17.4 | 133 | 43.6% (35.1, 52.1) |
| | sIgE: ≥ 17.5 | 27 | 81.5% (65.8, 97.1) |

*Selected for challenge based on previous detectable SPT wheal in the community but subsequently negative on repeat SPT in clinic (n=81; 54 of these were <3mm initially) or as negative control group with two negative skin prick tests (n=140)

**Below detection

†One sided, 97.5% confidence interval

Table 4: Relationship between family history of allergy and signs of allergy in the infant and age at introduction of peanut into the infant diet

| Family history of allergy and allergic symptoms in the infants prior to 12 months of age | N | Age at introduction of peanut | | | | | P* |
|------------------------------------------------------------------------------------------|------|-------------------------------|----------|----------|------------|---------------|--------|
| | | 4-6 mths | 7-8 mths | 9-10mths | 11-12 mths | Not yet given | |
| No risk factors | 2215 | 3.6% | 5.4% | 8.6% | 12.2% | 69.9% | |
| Family history of eczema or food allergy only (parents or siblings) | 1677 | 2.6% | 4.9% | 8.4% | 12.3% | 71.8% | 0.32 |
| Early eczema only (eczema \leq 6mths treated with topical steroids) | 418 | 1.8% | 4.4% | 6.9% | 8.2% | 78.2% | 0.014 |
| Early eczema and infant history of reaction to milk or egg (parent-reported) | 181 | 0.6% | 1.8% | 3.6% | 6.7% | 87.3% | <0.001 |

*Chi2 p value comparing the distribution of age at peanut introduction in each risk group to the baseline group of “no risk factors”

Table 5: Prevalence and types of community based adverse reactions to peanut in the first year of life in infants who introduced peanut at home prior to skin prick test screening at 12 months of age

| | Number introduced to peanut | % reporting a reaction | Reported reaction within 1 hour (possibly IgE-mediated)† | | | | | | | |
|-------------------------------------------------|-----------------------------|------------------------|------------------------------------------------------------|------------------------------------|-----------------------------------|------------------------------------|------------|------------------------------------|------------------------------|------------------------------------|
| | | | Skin only (hives, rash, swelling of lips, eyes or face) | | Gut only (vomiting, diarrhoea) | | Skin & gut | | Wheeze/ difficulty breathing | |
| | | | N | Challenge confirmed peanut allergy | N | Challenge confirmed peanut allergy | N | Challenge confirmed peanut allergy | N | Challenge confirmed peanut allergy |
| Low-risk group (no early eczema or egg allergy) | 1135 | 1.2% | 14 | 31% (4/13) | 0 | - | 0 | - | 0 | - |
| High-risk group (early eczema or egg allergy) | 185 | 9.7% | 15 | 67% (10/15) | 0 | - | 2 | 100% (2/2) | 1* | 0 |

* Reaction occurred on first reported introduction of peanut butter at 12 months of age. Vomiting also reported. Note – child had a negative SPT at age 12 months (1mm) and sIgE to peanut and a negative OFC to peanut at age 14 months in clinic, and tolerated peanut (1tsp per day) for a week at home post challenge with no reaction, so peanut allergy unlikely or outgrown. Child had positive SPT and sIgE to hazelnut at age 14 months.

† An additional 6 infants had a reported reaction occurring 1-4 hours after ingestion, with 5 involving skin only (1 positive on challenge) and 1 skin and gut (negative challenge). An additional 3 infants had a reported reaction > 4 hours after ingestion, all involving skin only (2 positive on challenge).

Table 6: Reactions to peanut on oral food challenge at 12 months of age

| Skin prick test wheal size | Number of peanut OFC | Number positive OFC | <u>Hives</u> [†] (% of positive challenges) | <u>Angioedema</u> [†] (% of positive challenges) | <u>Vomiting</u> [‡] (% of positive challenges) | <u>Skin & gut</u> [‡] (% of positive challenges) | <u>Anaphylaxis</u> ^{‡*} (% of positive challenges) |
|--------------------------------------------------------|----------------------|---------------------|---------------------------------------------------------|--------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------------|----------------------------------------------------------------|
| 0 mm | 221 | 0 | - | - | - | - | - |
| <u>Low risk group</u> (no early eczema or egg allergy) | | | | | | | |
| 1-4 mm | 43 | 2 (5%) [†] | 1 (50%) | 0 | 1 (50%) | 0 | 0 |
| 5-7 mm | 20 | 11 (55%) | 10 (91%) | 0 | 0 | 0 | 1 (9%) |
| >8mm | 23 | 20 (87%) | 17 (85%) | 3 (15%) | 1 (5%) | 1 (5%) | 0 |
| <u>High risk group</u> (early eczema or egg allergy) | | | | | | | |
| 1-4 mm | 94 | 8 (9%) [†] | 6 (75%) | 0 | 0 | 0 | 0 |
| 5-7 mm | 50 | 30 (60%) | 24 (80%) | 2 (7%) | 2 (7%) | 2 (7%) | 2 (7%) |
| >8mm | 69 | 65 (94%) | 59 (91%) | 13 (30%) | 10 (15%) | 10 (15%) | 3 (5%) |

* All infants developed respiratory symptoms (wheeze) and were treated with adrenaline (single dose in each cases) and Ventolin, +/- Zyrtec.

† 3 children in this category had a negative day 1 hospital based challenge but reacted on continued consumption of peanut at home, all with hives + eczema flare +/- angioedema – these reactions are not presented in the table but the infants are included in the “number positive OFC” column.

‡ Note that categories are not mutually exclusive, e.g. all of the children with skin & gut reaction also appear in both the skin (hives or angioedema) and gut (vomiting) columns

Figure Legends

Figure 1: Characterizing peanut SPT wheal size and specific IgE levels in a population based sample of infants, stratified by high risk (early eczema and/or egg allergy) or low risk (no early eczema and/or egg allergy) groups. (a) Proportion of infants sensitized to peanut on community-based skin prick test. (b) Relationship between skin prick and sIgE results to peanut among infants attending food challenge clinic. (c) Relationship between peanut skin prick results and challenge outcome among infants attending food challenge clinic.* (d) Relationship between peanut sIgE results and challenge outcome among infants attending food challenge clinic.

**Infants with a 0mm SPT wheal for peanut included infants selected for challenge based on previous detectable SPT wheal in the community (n=81; 54 of these were <3mm) or as part of a negative control group (0mm skin prick test to peanut in both community and clinic, n=140). Numbers in each analysis differ due to the study design: skin prick testing to peanut was performed as a screening step for all infants, but only infants attending challenge clinic had blood taken for sIgE measurement (83% of those attending clinic agreed to give a blood sample).*

Figure 2: Cases of peanut allergy that may be theoretically preventable by applying the LEAP intervention findings to a general infant population[†]

[†] We used a hypothetical population of 1,000 infants to represent the general population. At each step, we used the best available observed data from either HealthNuts (blue; this study) or LEAP (black) [1] to calculate the proportion of this hypothetical population that would fall into each group, and the prevalence of peanut allergy in each group. Precedence was given to data from the LEAP study where available.

* The proportion of peanut allergy cases predicted to develop in the 0-4mm SPT group without intervention is the observed proportion of children with peanut allergy in the control arm of the LEAP study. This may be higher than actually observed in a “real world” setting since some of these children might have been introduced to peanut earlier if they were not participating in this randomized trial and thus instructed to avoid peanut until age 5 years. The proportion of peanut allergy cases predicted to develop in the 0-4mm SPT group with intervention is the observed proportion of children with peanut allergy in the intervention arm of LEAP in the intention to treat analysis.

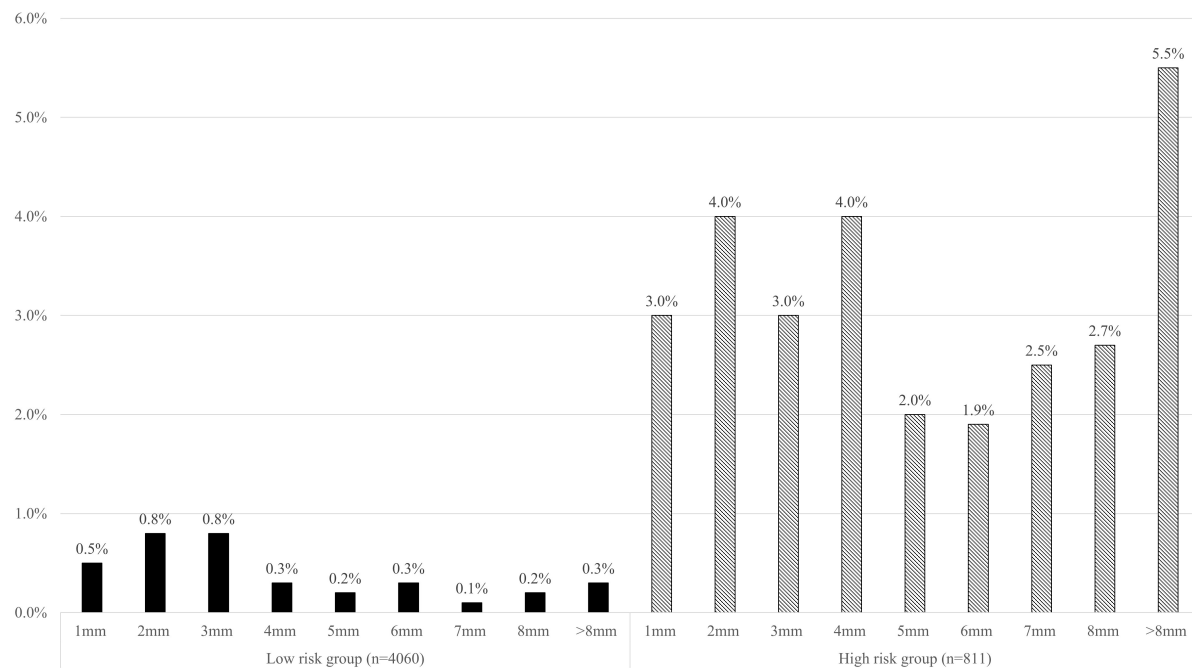
[‡] We used figures from the LEAP study [1] to estimate the proportion of high risk infants who would have a SPT>4mm to peanut at 4-11 months of age. This figure (10.6%) is somewhat lower than the proportion of high risk infants in HealthNuts with a SPT>4mm (14.6%), possibly because infants in HealthNuts were older at the time of SPT (12 months of age)

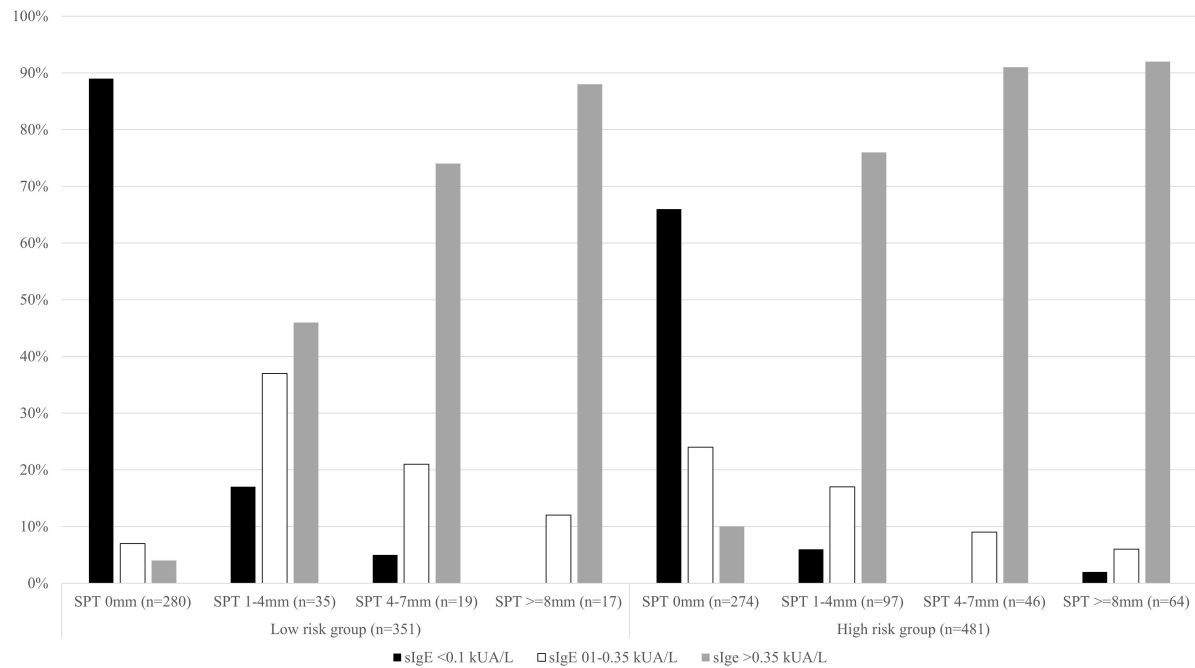
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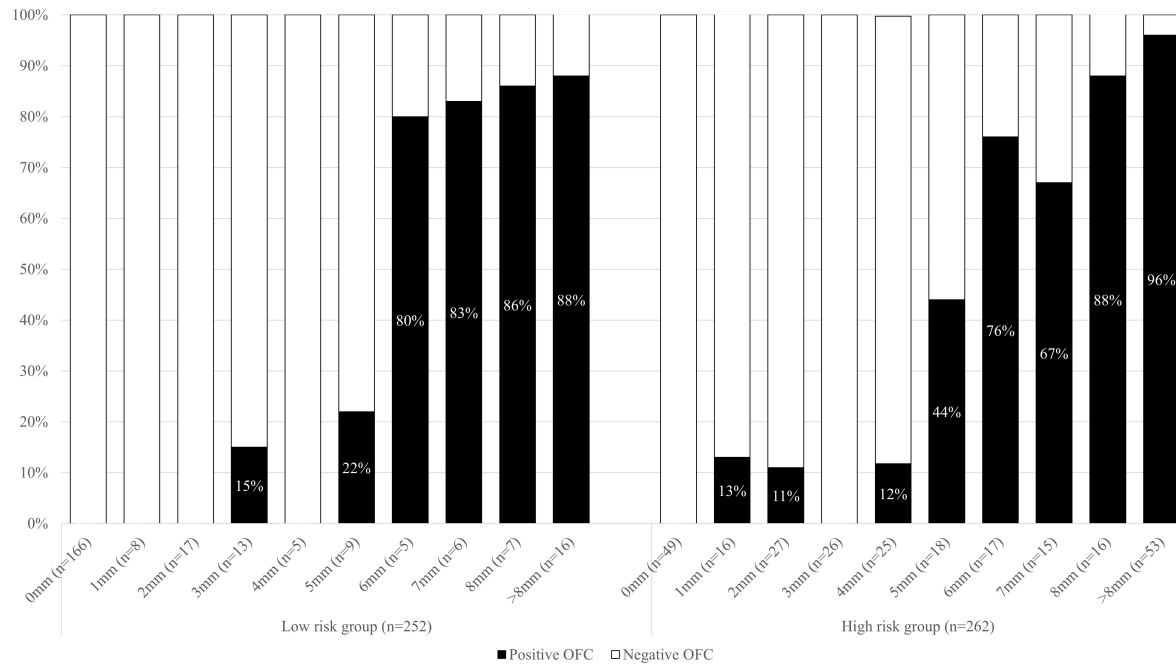
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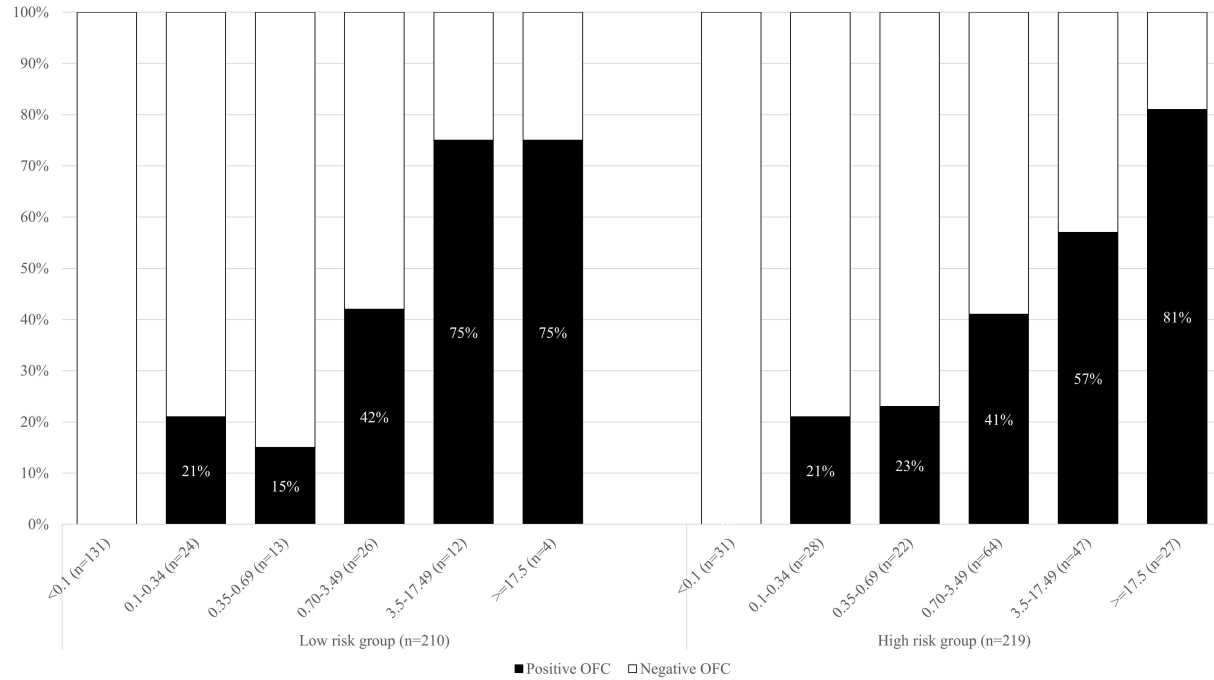
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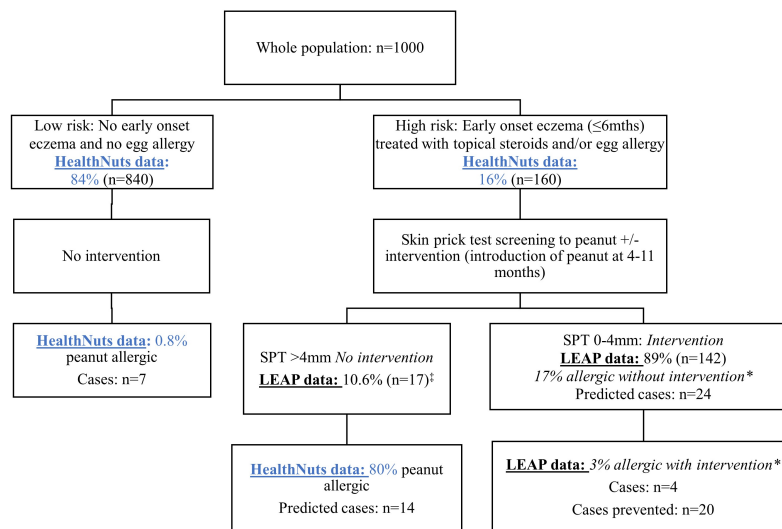
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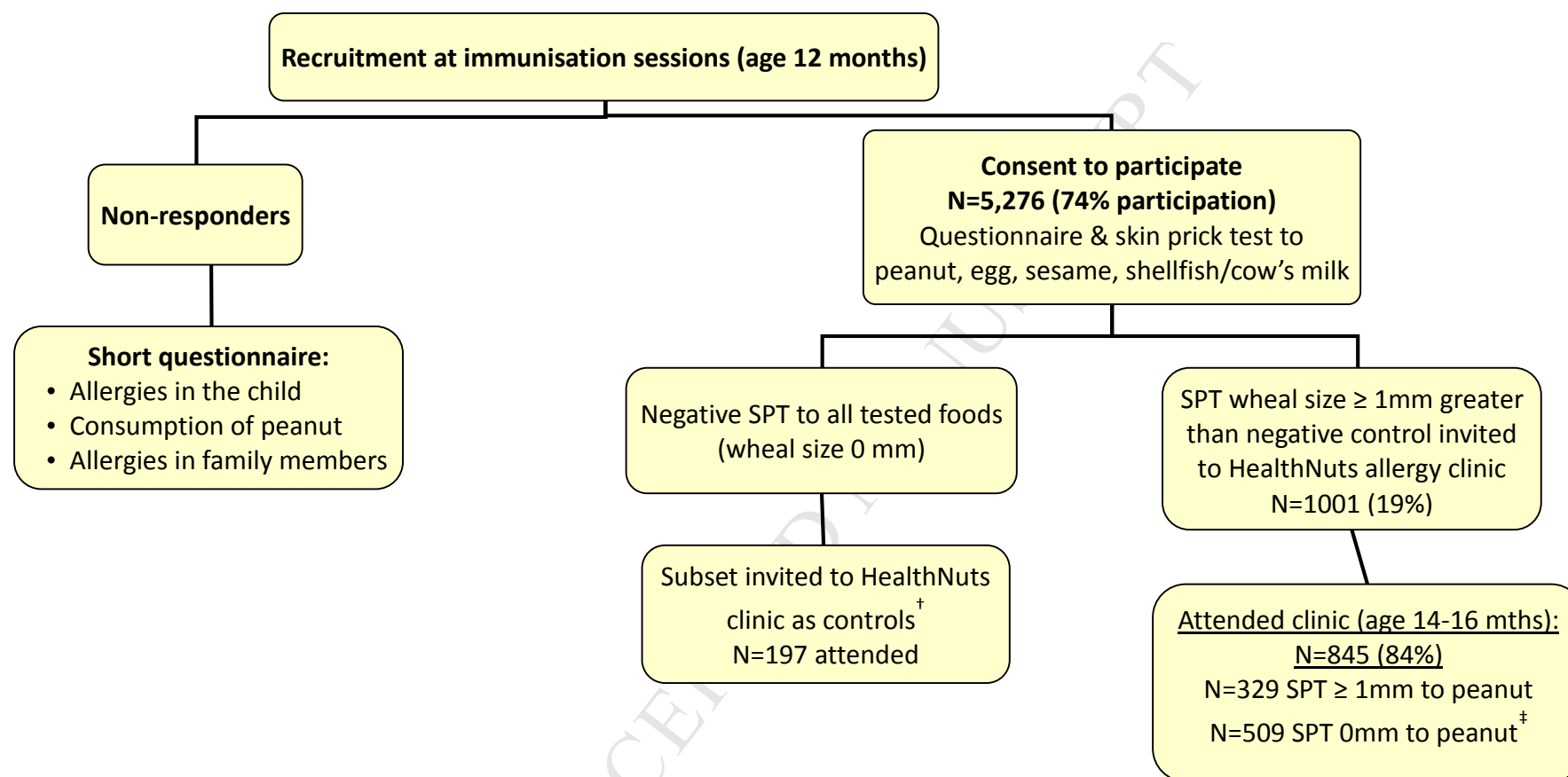








Supplementary Figure E1:



[†] Non-sensitised controls for lab studies. Food challenged to either egg or peanut, and blood collected for sIgE measurement, immunology etc.

[‡] 86 of these infants had a peanut SPT ≥ 1 mm at recruitment, thus had peanut OFC despite negative SPT at clinic. The remainder attended clinic due to sensitisation to other foods (not peanut) and did not undergo peanut challenge.

Online Repository Material

Table E1: Comparison of definitions of high risk for development of peanut allergy used in the LEAP

randomized controlled trial and subsequent editorials and consensus guidelines

| | LEAP randomized controlled trial | Editorial accompanying the LEAP study | Consensus guidelines |
|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Age range targeted | 4-11 months | 4-8 months | 4-11 months |
| Eczema definition | <p>Severe eczema (89% of participants):</p> <p>Requires application of topical creams, ointments, or both containing corticosteroids or calcineurin inhibitors and that, if the participant is <6 months of age, lasted for at least 12 of 30 days on 2 occasions or, if the participant is >6 months of age, lasted for at least 12 of 30 days on 2 occasions in the last 6 months</p> <p>OR</p> <p>Is currently or was previously graded ≥ 40 by using the modified SCORAD evaluation</p> | <p>“Any infant between 4 months and 8 months of age <i>believed to be at risk for peanut allergy</i>”</p> | <p>Severe eczema as per LEAP definition. If occurring in first 4 to 6 months of life – “might benefit from evaluation by an allergist”</p> |
| Egg allergy definition | <p>Egg allergy (64% of participants):</p> <p>SPT wheal ≥ 6mm to raw hen’s egg white and no history of previous egg tolerance</p> <p>OR</p> <p>SPT wheal ≥ 3mm to pasteurized hen’s egg white and allergic symptoms related to exposure to hen’s egg</p> | As above | <p>Egg allergy as per LEAP definition. If occurring in first 4 to 6 months of life - “might benefit from evaluation by an allergist”</p> |
| Peanut SPT cut-offs and recommendations | <p>0-4mm: Included</p> <p>>4mm: Excluded</p> | <p>0mm: Start peanut containing diet</p> <p>1-4mm: Peanut challenge – if negative, start peanut containing diet</p> <p>>4mm: No recommendations</p> | <p>Clinician can perform an observed peanut challenge for those with evidence of a positive peanut skin test response to determine whether they are clinically reactive before initiating at-home peanut introduction</p> |